09/734,002

Set	Items	Description
S1	1088	AU="SEIKI M" OR AU="SEIKI M."
S2	234	AU="SEIKI MOTOHARU"
S3	17626	AU="SATO H"
S4	3257	AU="SATO H."
S5	12400	AU="SATO HIROSHI"
S6	363	AU="SHINAGAWA A" OR AU="SHINAGAWA A." OR AU="SHINAGAWA AKIRA"
S7	34349	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	61118	METALLOPROTEINASE
S9	837	S7 AND S8
S10	37155	MATRIX(W)METALLOPROTEINASE
S11	737	S7 AND S10
S12	12810	MMP(W)2
S13	5944	S10(W)2
S14	13230	MEMBRANE(W)TYPE
S15	881	MT(W)MMP
S16	273	S11 AND S12
S17	125	S11 AND S13
S18	289	S16 OR S17
S19	13454	S14 OR S15
S20	238	S18 AND S19
S21	67	RD (unique items)
S22	57069	TYPE(W)3
S23	21	MT(W)MMP(W)3
S24	432	S8 AND S22
S25	114734	COLLAGENASE OR GELATINASE OR STROMELYSIN OR MATRILYSIN
S26	726	S22 AND S25
S27	857	S24 OR S26
S28	185	S27 NOT PY>1995
S29	168	RD (unique items)
S30	0	23 RD
S31	0	S23 NOT PY>1995
S32	0	RD (unique items)
S33	243	S22(S)S25
S34	159	S8(S)S22
S35		

21/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09463313 97301604 PMID: 9158005
Expression and tissue localization of membrane-types 1, 2, and 3 matrix metalloproteinases in human invasive breast carcinomas.
Ueno H; Nakamura H; Inoue M; Imai K; Noguchi M; **Sato H** ; **Seiki M** ; Okada Y
Department of Molecular Immunology, School of Medicine, Kanazawa University, Ishikawa, Japan.
Cancer research (UNITED STATES) May 15 1997, 57 (10) p2055-60, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Activation of the zymogen of **matrix metalloproteinase 2** (proMMP-2, progelatinase A) possibly is one of the key steps in invasion and metastasis of various human carcinomas. Three different **membrane - type** MMPs (MT-MMPs), MT1-, MT2-, and MT3-MMPs are thought to be activators of proMMP-2 in the tissues. MT4-MMP is structurally different from the other three enzymes, and its function as proMMP-2 activator is uncertain. In the present study of human invasive breast carcinomas, we examined a correlation between the expression of MT1-, MT2-, and MT3-MMPs, immunolocalization of MT1- and MT2-MMPs, and proMMP-2 activation. Northern blot analysis demonstrated the predominant expression of MT1-MMP mRNA in carcinoma tissues (20 of 20 cases), whereas MT2-MMP was detected in only 25% of the cases (5 of 20 cases), and no detectable expression of MT3-MMP was observed. The expression levels of MT1-MMP but not MT2-MMP correlated well with the presence of lymph node and distant metastases, clinical stages, and size of tumors. Immunohistochemically, MT1-MMP was localized predominantly in the carcinoma cells in all of the samples (32 of 32 cases). Immunostaining of MT2-MMP in the carcinoma cells was observed in only 38% of the cases (12 of 32 cases). Immunoblot analysis of tumor homogenates confirmed the presence of these MT-MMPs. Activation of proMMP-2 was significantly higher in the carcinoma samples with lymph node or distant metastasis compared to carcinoma without metastasis, normal control, or fibrocystic disease ($P < 0.05$). An increase in the activation ratio of proMMP-2 correlated directly with the expression of MT1-MMP but not MT2-MMP, as measured by either Northern blot analysis or immunostaining. These results suggest that MT1-MMP may play a key role in human breast carcinoma invasion and metastasis by being predominantly responsible for activation of proMMP-2.

21/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09227083 96338604 PMID: 8743942
MT - MMP , **the cell surface activator of proMMP-2 (pro-gelatinase A), is expressed with its substrate in mouse tissue during embryogenesis.**
Kinoh H; **Sato H** ; Tsunezuka Y; Takino T; Kawashima A; Okada Y; **Seiki M**
Departments of Molecular Virology & Oncology, Kanazawa University, Ishikawa, Japan.
Journal of cell science (ENGLAND) May 1996, 109 (Pt 5) p953-9, ISSN 0021-9533 Journal Code: HNK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Matrix metalloproteinases (MMPs), which degrade the components of the extracellular matrix, are key enzymes involved in the tissue remodeling of multicellular organisms. Since MMPs are secreted as inactive zymogens (pro-MMPs), they have to be activated to function. We identified a **membrane - type** MMP (**MT - MMP**) that activated proMMP-2 (pro-gelatinase A = 72 kDa type IV pro-collagenase) and described its expression on the invasive tumor cell surface. In this study we further examined the

expression and role of **MT - MMP** in the activation of proMMP-2 during mouse embryogenesis. Northern blotting demonstrated that **MT - MMP** expression was increased together with that of **MMP - 2** and its inhibitor gene, TIMP-2, in embryos depending upon the number of days after gestation, and decreased with maturation after birth. In situ hybridization and immunohistochemistry localized **MT - MMP** mRNA and protein in the cells of ossifying tissues where both **MMP - 2** and TIMP-2 were expressed. Activated **MMP - 2** was detected by gelatin zymography in the lysates prepared from the micro dissected tissues that expressed the three genes. The activation rate of proMMP-2 was proportional to the expression of **MMP - 2** and **MT - MMP** . These results indicated that proMMP-2 activation through its activator, **MT - MMP** , is a physiological system used by organisms to initiate tissue remodeling on the cell surface.

21/3,AB/46 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11920519 BIOSIS NO.: 199900166628
Expression and tissue localization of membrane - type **1, 2, and 3 matrix metalloproteinases in human astrocytic tumors.**
AUTHOR: Nakada Mitsutoshi; Nakamura Hiroyuki; Ikeda Eiji; Fujimoto Noboru; Yamashita Junkoh; **Sato Hiroshi** ; **Seiki Motoharu** ; Okada Yasunori(a
AUTHOR ADDRESS: (a)Dep. Pathol., Sch. Med., Keio Univ., 35 Shinanomachi, Shinjuku-ku, Tokyo 160-0016**Japan
JOURNAL: American Journal of Pathology 154 (2):p417-428 Feb., 1999
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Three different **membrane - type** matrix metalloproteinases (MT1-, MT2-, and MT3-MMPs) are known to activate in vitro the zymogen of **MMP - 2** (pro- **MMP - 2** , progelatinase A), which is one of the key MMPs in invasion and metastasis of various cancers. In the present study, we have examined production and activation of pro- **MMP - 2** , expression of MT1-, MT2-, and MT3-MMPs and their correlation with pro- **MMP - 2** activation, and localization of **MMP - 2** , MT1-MMP, and MT2-MMP in human astrocytic tumors. The sandwich enzyme immunoassay demonstrates that the production levels of pro- **MMP - 2** in the anaplastic astrocytomas and glioblastomas are significantly higher than that in the low-grade astrocytomas ($P < 0.05$ and $P < 0.01$, respectively), metastatic brain tumors ($P < 0.05$), or normal brains ($P < 0.01$). Gelatin zymography indicates that the pro- **MMP - 2** activation ratio is significantly higher in the glioblastomas than in other astrocytic tumors ($P < 0.01$), metastatic brain tumors ($P < 0.01$), and normal brains ($P < 0.01$). The quantitative reverse transcription polymerase chain reaction analyses demonstrate that MT1-MMP and MT2-MMP are expressed predominantly in glioblastoma tissues (17/17 and 12/17 cases, respectively), and their expression levels increase significantly as tumor grade increases. MT3-MMP is detectable in both astrocytic tumor and normal brain tissues, but the mean expression level is approximately 50-fold lower compared with that of MT1-MMP and MT2-MMP in the glioblastomas. The activation ratio of pro- **MMP - 2** correlates directly with the expression levels of MT1-MMP and MT2-MMP but not MT3-MMP. In situ hybridization indicates that neoplastic astrocytes express MT1-MMP and MT2-MMP in the glioblastoma tissues (5/5 cases and 5/5 cases, respectively). Immunohistochemically, MT1-MMP and MT2-MMP are localized to the neoplastic astrocytes in glioblastoma samples (17/17 cases and 12/17 cases, respectively), which are also positive for **MMP - 2** . In situ zymography shows gelatinolytic activity in the glioblastoma tissues but not in the normal brain tissues. These results suggest that both MT1-MMP and MT2-MMP play a key role in the activation of pro- **MMP - 2** in the human malignant astrocytic tumors and that the gelatinolytic activity is involved in the astrocytic tumor invasion.

1999

21/3,AB/47 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11700646 BIOSIS NO.: 199800482377
Expression and tissue localization of membrane-types 1,2, and 3 matrix metalloproteinases in human urothelial carcinomas.
AUTHOR: Kitagawa Yasuhide; Kunimi Kazuto(a); Ito Hideaki; **Sato Hiroshi** ; Uchibayashi Tadao; Okada Yasunori; **Seiki Motoharu** ; Namiki Mikio
AUTHOR ADDRESS: (a)Dep. Urol., Kanazawa Univ. Sch. Med., Takara-machi, 13-1 Kanazawa 920**Japan
JOURNAL: Journal of Urology 160 (4):p1540-1545 Oct., 1998
ISSN: 0022-5347
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: Three different **membrane - type** matrix metalloproteinases (MT1, 2, 3-MMP) which can activate proMMP-2 (progelatinase A) are thought to have an important role in various human carcinoma invasions and metastases. We examined the mRNA expression of MT-MMPs and the tissue immunolocalization of MT1-MMP in human urothelial carcinomas. Materials and Methods: mRNA was extracted from 27 clinical urothelial carcinomas and 10 normal urothelial mucosa tissues remote from the tumor. RT-PCR using specific primers was performed, and PCR products were hybridized to 32P-labeled internal probes and analyzed by a bioimage analyzer. Immunolocalization was studied using a monoclonal antibody against MT1-MMP (114-6G6). Results: MT1-MMP and MT2-MMP mRNA expressions in urothelial carcinomas were significantly higher than those in the normal mucosa. In contrast, MT3-MMP mRNA was little expressed in both tissues, and the amount of MT3-MMP mRNA appeared to be much lower than MT1-MMP and MT2-MMP in the tissue samples. In terms of the tumor multiplicity, MT1-MMP and MT2-MMP mRNA expressions in the group of multiple tumors were significantly higher than those in the solitary tumor group. The carcinoma cells were immunostained for MT1-MMP predominantly in invasive and superficial carcinoma cells. The immunoreactivity was more intense in the invasive type than in the superficial type. Conclusions: It is suggested that MT1-MMP and MT2-MMP play an important role in the development of human urothelial carcinomas and reflect some aspects of the pathogenesis of multifocal occurrence. In spite of the possible contribution to the invasive and metastatic phenotype, MT1-MMP mRNA and its product are thought to be expressed already in the clinical superficial stage in some cases of this tumor type.

1998

21/3,AB/62 (Item 2 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3465327 IFI Acc No: 0106947
Document Type: C
PROTEIN AND MONOCLONAL ANTIBODY SPECIFIC THERETO; ISOLATED MATRIX METALLOPROTEINASE **OF GIVEN AMINO ACID SEQUENCE HAVING THE ACTIVATION CAPABILITY OF PRO-** MATRIX METALLOPROTEINASE 2 **; VECTORS; TRANSFORMED CELLS; USE IN DIAGNOSIS OF CANCER**
Inventors: **Sato Hiroshi** (JP); **Seiki Motoharu** (JP); **Shinagawa Akira** (JP
Assignee: Fuji Yakuhin Kogyo K K JP
Assignee Code: 21367

Publication (No,Date), Applic (No,Date):
Publication (Kind,No,Date), Applic (No,Date):
US 6191255 20010220 US 9841 19980220
1919
Calculated Expiration: 20160712
PCT Pub(No,Date),Applic(No,Date): WO 974080 19970206 WO 96JP1956
19960712
Section 371: 19980220
Section 102(e):19980220
Priority Applic(No,Date): JP 95200319 19950714; JP 95200320 19950714
Abstract: A novel protein which is useful as a diagnostic means for studies relating to the diagnosis and treatment of cancer (detection of cancer cells, estimation of the malignity, etc.) and for other medicinal and physiological purposes; a gene encoding the same; and an antibody, in particular, a monoclonal antibody specific to the protein. **MT - MMP** -3, which is a pro **MMP - 2** activator having the ability to activate pro **MMP - 2** which is under expression specifically on the surface layer of a human cancer cell and falling within the category of MMP but being different from **MT - MMP** -1; a DNA containing the base sequence encoding the same; host cells transformed by the DNA; a process for producing a **matrix metalloproteinase** protein by using the host cells; a monoclonal antibody binding specifically to the **matrix metalloproteinase** protein; and use of the protein and antibody.
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Set     Items   Description
S1       1088   AU="SEIKI M" OR AU="SEIKI M."
S2        234   AU="SEIKI MOTOHARU"
S3      17626   AU="SATO H"
S4       3257   AU="SATO H."
S5      12400   AU="SATO HIROSHI"
S6        363   AU="SHINAGAWA A" OR AU="SHINAGAWA A." OR AU="SHINAGAWA AKI-
          RA"
S7      34349   S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8      61118   METALLOPROTEINASE
S9        837   S7 AND S8
S10     37155   MATRIX(W)METALLOPROTEINASE
S11       737   S7 AND S10
S12     12810   MMP(W)2
S13      5944   S10(W)2
S14     13230   MEMBRANE(W)TYPE
S15       881   MT(W)MMP
S16       273   S11 AND S12
S17       125   S11 AND S13
S18       289   S16 OR S17
S19     13454   S14 OR S15
S20       238   S18 AND S19
S21        67   RD (unique items)
S22     57069   TYPE(W)3
S23        21   MT(W)MMP(W)3
S24       432   S8 AND S22
S25    114734   COLLAGENASE OR GELATINASE OR STROMELYSIN OR MATRILYSIN
S26       726   S22 AND S25
S27       857   S24 OR S26
S28       185   S27 NOT PY>1995
S29       168   RD (unique items)
S30         0   23 RD
S31         0   S23 NOT PY>1995
S32         0   RD (unique items)
S33       243   S22(S)S25
S34       159   S8(S)S22
S35       328   S33 OR S34
S36        55   S35 NOT PY>1995
S37        41   RD (unique items)
?
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37/3,AB/13 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03910085 BIOSIS NO.: 000075088158
PRODUCTION AND CHARACTERIZATION OF A MONO CLONAL ANTIBODY TO HUMAN TYPE IV COLLAGEN
AUTHOR: SAKAI L Y; ENGVALL E; HOLLISTER D W; BURGESON R E
AUTHOR ADDRESS: DEP. OF PEDIATRICS, HARBOR-UCLA MED. CENT., BUILD. C-3, 1000 WEST CARSON STREET, TORRANCE, CALIF. 90509.
JOURNAL: AM J PATHOL 108 (3). 1982. 310-318. 1982
FULL JOURNAL NAME: American Journal of Pathology
CODEN: AJPAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A monoclonal antibody to human basement membrane Type IV collagen was produced. The antibody reacts with the pepsin-resistant, collagenase-sensitive domain of Type IV collagen isolated from placental membranes, but not with human collagens of Types I, II, III, V, 1.alpha., 2.alpha. and 3.alpha.. The antibody precipitates biosynthetically labeled human Type IV procollagen, and the preciptate contains both both the .alpha.1 (IV) and .alpha.2 (IV) chains, suggesting the occurrence of these chains within the same triple-helical molecule. When used in indirect immunofluorescence, the antibody gives brilliant staining of basement membranes from a variety of human tissues but does not stain tissues of bovine, canine, rabbit, rat or mouse origin. This antibody may be of value in research on the structure of human basement membrane collagen, on the distribution of this collagen in various basement membranes, and particularly for the study of basement membranes in normal human development and pathologic processes.

1982

37/3,AB/20 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

123078447 CA: 123(7)78447d PATENT
Human tissue inhibitor of metalloproteinase type three (TIMP-3), its therapeutic uses and cloning of a cDNA encoding it
INVENTOR(AUTHOR): Silbiger, Scott M.; Koski, Raymond A.
LOCATION: USA
ASSIGNEE: Amgen Inc.
PATENT: European Pat. Appl. ; EP 648838 A1 DATE: 950419
APPLICATION: EP 94115578 (941004) *US 134231 (931006)
PAGES: 62 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C12N-015/15A; C07K-014/81B; C12N-001/21B; C12N-005/10B; A61K-048/00B; A61K-038/57B; A61K-038/43B; A61K-038/17B; A61K-038/48B; C07K-016/38B
DESIGNATED COUNTRIES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE

37/3,AB/21 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

109205926 CA: 109(23)205926x JOURNAL
The complete primary structure of human matrix metalloproteinase-3. Identity with stromelysin
AUTHOR(S): Saus, Juan; Quinones, Susan; Otani, Yoshihide; Nagase, Hideaki ; Harris, Edward D., Jr.; Kurkinen, Markku
LOCATION: Robert Wood Johnson Med. Sch., Univ. Med. Dent., Piscataway, NJ , 08854, USA

JOURNAL: J. Biol. Chem. DATE: 1988 VOLUME: 263 NUMBER: [redacted] PAGES: 6742-5 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

37/3,AB/26 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00676981
Tissue inhibitor of metalloproteinase type three (TIMP-3).
Gewebeinhibitor fur Metalloproteasen Type 3 (TIMP-3).
Inhibiteur de metalloproteases d'origine tissulaire du type 3 (TIMP-3).
PATENT ASSIGNEE:
AMGEN INC., (923233), Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
INVENTOR:
Silbiger, Scott M, 21520 Burbank Boulevard No.114, Woodland Hills, California 91367, (US)
Koski, Raymond A., 7 Meeting House Lane, Old Lyme Road, Connecticut 06371, (US)
LEGAL REPRESENTATIVE:
Vossius, Volker, Dr. et al (12524), Dr. Volker Vossius Patentanwaltskanzlei - Rechtsanwaltskanzlei Holbeinstrasse 5, D-81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 648838 A1 950419 (Basic)
APPLICATION (CC, No, Date): EP 94115578 941004;
PRIORITY (CC, No, Date): US 134231 931006
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/15; C07K-014/81; C12N-001/21; C12N-005/10; A61K-048/00; A61K-038/57; A61K-038/43; A61K-038/17; A61K-038/48; C07K-016/38;

ABSTRACT EP 648838 A1
Provided herein are metalloproteinase inhibitors and polynucleotides encoding such factors. In particular, provided herein are novel mammalian tissue inhibitors of metalloproteinase (designated as type three, or "TIMP-3"), fragments, derivatives, and analogs thereof, polynucleotides encoding the same and methods of producing recombinant TIMP-3's. In a further aspect, pharmaceutical compositions and kits containing TIMP-3's and their use for treating disorders are provided herein. In yet another aspect, antibodies selectively binding TIMP-3's are provided.
ABSTRACT WORD COUNT: 73

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPAB95	1536
SPEC A	(English)	EPAB95	13884
Total word count - document A			15420
Total word count - document B			0
Total word count - documents A + B			15420

37/3,AB/30 (Item 4 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00291769
TISSUE INHIBITOR METALLOPROTEINASE TYPE THREE (TIMP-3)
INHIBITEURS TISSULAIRES DE LA METALLOPROTEASE TYPE TROIS (TIMP-3)
Patent Applicant/Assignee:
AMGEN INC,
Inventor(s):
SILBIGER Scott M,

KOSKI Raymond A,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9509918 A1 19950413
Application: WO 94US11241 19941004 (PCT/WO US9411241)
Priority Application: US 93134231 19931006
Designated States: AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KP KR KZ LK LT LU LV MG MN MW NL NO NZ PL PT RO RU SD SE SK UA UZ VN AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 19418

English Abstract

According to the present invention, a class of novel tissue inhibitors of metalloproteinase are provided. For convenience, the present polypeptides are referred to as "TIMP-3", as these polypeptides represent a new class of members of the tissue inhibitors of metalloproteinases. Also provided are DNA sequences coding for all or part of the present TIMP-3's, vectors containing such DNA sequences, and host cells transformed or transfected with such vectors. Also comprehended by the invention are methods of producing recombinant TIMP-3's, and methods of treating disorders. Additionally, pharmaceutical compositions including TIMP-3's and antibodies selectively binding TIMP-3's are provided.

French Abstract

La presente invention concerne une categorie de nouveaux inhibiteurs tissulaires de la metalloprotease. Par commodite, les popypeptides presentes sont appeles "TIMP-3" car ils representent une nouvelle categorie d'inhibiteurs tissulaires de la metalloprotease. L'invention a egalement pour objet des sequences d'ADN codant pour tout ou partie des TIMP-3 presentes, des vecteurs contenant des sequences d'ADN de ce type, et des cellules hotes transformees ou transfectees avec ces vecteurs. L'invention traite, en outre, de procedes de production de TIMP-3 de recombinaison, et des procedes pour traiter ces troubles. Par ailleurs, des compositions pharmaceutiques comprenant des TIMP-3 et des anticorps liant selectivement les TIMP-3 sont decrits.
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